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Treatment of severe ulcerative colitis: differences in elderly patients?

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Abstract: Almost as many as 10% of patients with ulcerative colitis have late onset with the first flare occurring at 60-70 years of age. The course of the disease and the basic principles of management in geriatric populations do not differ from those in younger patients. However, elderly patients pose distinct problems in therapy choice. In middle-aged patients untreated severe ulcerative colitis has been reduced to <1% in specialized centers at the present time but is still high in the elderly. In general, the management requires close collaboration between gastroenterologists and surgeons. In adult patients, current evidence supports initial treatment with intravenous steroids. However, only 40% of patients show complete response after corticosteroid therapy and almost 30% come to colectomy. Cyclosporine still has a first place as salvage therapy because of its short half-life and its established short-term efficacy in about 70% of patients who fail steroids. The drug should be avoided in frail or elderly patients (especially over 80 years old) with significant comorbidity, and also where colectomy is likely to be necessary in the short to medium term. The long-term benefit of this therapy remains unsatisfactory as colectomy is often only delayed. Infliximab is the choice for those patients with a less severe colitis and less likelihood of urgent colectomy. Tacrolimus has only been used in one randomized controlled trial with similar results to cyclosporine. Surgery is still the definitive procedure for the treatment of ulcerative colitis in adult patients, and its timing is of paramount importance.

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Treatment of Severe Ulcerative Colitis: Differences in Elderly Patients?

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Key Words

Ulcerative colitis • Cyclosporine • Infliximab

Abstract

Almost as many as 10% of patients with ulcerative colitis have late onset with the first flare occurring at 60–70 years of age. The course of the disease and the basic principles of management in geriatric populations do not differ from those in younger patients. However, elderly patients pose distinct problems in therapy choice. In middle-aged patients untreated severe ulcerative colitis has been reduced to <1% in specialized centers at the present time but is still high in the elderly. In general, the management requires close collaboration between gastroenterologists and surgeons. In adult patients, current evidence supports initial treatment with intravenous steroids. However, only 40% of patients show complete response after corticosteroid therapy and almost 30% come to colectomy. Cyclosporine still has a first place as salvage therapy because of its short half-life and its established short-term efficacy in about 70% of patients who fail steroids. The drug should be avoided in frail or elderly patients (especially over 80 years old) with significant comorbidity, and also where colectomy is likely to be necessary in the short to medium term. The long-term benefit of this therapy remains unsatisfactory as colectomy is often only delayed. Infliximab is the choice for those patients with a less severe colitis and less likelihood of urgent colectomy. Tacrolimus has only been used in one randomized controlled

trial with similar results to cyclosporine. Surgery is still the definitive procedure for the treatment of ulcerative colitis in adult patients, and its timing is of paramount importance.

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Introduction

Ulcerative colitis (UC) exhibits bimodality in age-specific incidence rates with the second peak occurring at 60–70 years of age [1–5]. Almost as many as 10% of patients with UC have late onset [6]. The course of the disease and the basic principles of management in geriatric populations do not differ from those in younger patients. However, elderly patients pose distinct problems in therapy choice. Since patients older than 60 years are excluded from most therapeutic trials on severe UC, the treating physician is left with many open questions for the elderly patient with UC. Unfortunately, even the current ECCO guidelines on UC do not live up to expectations [7–9]. Guidelines appear most necessary where evidence is limited, and therefore such guidelines should cover more special situations such as treatment of the elderly patient. The aim of this article is to summarize the literature on medical treatment of severe UC focusing on (1) the age of the patients included in the respective studies, and (2) finding age-specific characteristics in current medical trials.

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Table 1. Therapy options in patients with moderate and severe UC

| Author | Drug | Regime | Study type | Year | Patients | Response/remission | Age (range) | Study period |
|--|-------|--|----------------------|------|---|---|-------------|--|
| <i>Intensive intravenous steroid treatment (IIVST)</i> | | | | | | | | |
| Truelove [10] | IIVST | cortisone 100 mg/day i.v. | Controlled trial, pc | 1955 | 210 (109 cortisone, 101 P) | remission 45/109 = 41% (vs. 16% in P) response 30/109 = 27% (vs. 24% in P) no change/worse 34/109 = 31% (vs. 60% P) | NA | 6 weeks |
| Truelove [11] | IIVST | prednisolone 60 mg/day i.v. hydrocortisone 100 mg rectally/day | Case series | 1974 | 49 | remission 36/49 = 73% response 4/49 = 8% no change/worse 9/49 = 18% | NA | 5 days |
| Truelove [12] | IIVST | prednisolone 60 mg/day i.v. hydrocortisone 100 mg rectally/day | Case series | 1978 | 100 | remission 60/100 = 60% response 15/100 = 15% no change/worse 25/100 = 25% | 5–84 | 5 days |
| Meyers [23] | IIVST | hydrocortisone 300 mg/day vs. corticotropin 120 U/day i.v. | RCT, db | 1983 | 66 | remission 28/66 = 42% | | 10 days |
| <i>Cyclosporine A (CyA)</i> | | | | | | | | |
| Lichtiger [14] | CyA | 4 mg/kg vs. placebo | RCT, db | 1994 | 20 (11 CyA, 9 P) | response CyA: 9/11 = 82% P: 0/9 = 0% | 34 (18–60) | 7 days |
| D'Haens [15] | CyA | 4 mg/kg vs. 40 mg M-pred | RCT, db | 2001 | 30 (14 CyA, 15 M-pred, 1 DA) | response: CyA: 9/14 = 64% M-pred: 8/15 = 53% | 36 (20–67) | 8 days |
| <i>Infliximab (IFX)</i> | | | | | | | | |
| Järnerot [17] | IFX | 1 × 5 mg/kg | RCT, db | 2005 | 45 (24 IFX, 21 P) | colectomy rate IFX: 7/24 = 29% P: 14/21 = 67% | 37 (19–61) | 3 months |
| Ochsenkühn [38] | IFX | 5 mg/kg week 0/2/6 vs. prednisolone 1.5 mg/kg | RCT, db | 2004 | 13 (6 IFX, 7 prednisolone) | response: IFX: 5/6 = 83% prednisolone: 6/7 = 85% | 31 (21–44) | 13 weeks |
| Probert [39] | IFX | 5 mg/kg week 0/2 | RCT, pc | 2003 | 43 (23 IFX, 20 P) | remission: IFX 9/23 = 39% P 6/20 = 30% | 41 (29–50) | 8 weeks |
| Rutgeerts [36] | IFX | 5 mg/kg, 10 mg/kg, placebo at week 0/2/6 then every 8 weeks | RCT, db | 2005 | 364 (ACT1) 364 (ACT2): 121 P, 121 IFX 5 mg/kg, 121 IFX 10 mg/kg | ACT1 week 8 response: IFX 69% 5 mg/kg vs. 37% placebo ACT2 week 8: IFX 64% 5 mg/kg vs. 29% placebo | 42 | ACT 1: 46 weeks ACT 2: 22 weeks |
| Sands [40] | IFX | 5 mg/kg, 10 mg/kg, 20 mg/kg, placebo | RCT, db | 2001 | 11 8 IFX, 3 P | response: IFX 4/8 = 50% P: 0/3 = 0% | 37 31–63 | 2 weeks |
| Armuzzi [37] | IFX | 5 mg/kg at week 0/2/6 then every 8 weeks; M-pred 0.7–1 mg/kg/day | RCT, open-label | 2004 | 20 10 IFX, 10 M-pred | remission | 24–53 | 2 weeks |
| <i>Tacrolimus (Tacro)</i> | | | | | | | | |
| Ogata [18] | Tacro | 0.05 mg/kg/day | RCT, db | 2006 | 65 21 high conc. (10–15 ng/ml) 22 low conc. (5–10 ng/ml), 20 P | response: high conc.: 13/19 = 68% low conc.: 8/21 = 38% P: 2/20 = 10% | 33 | 2 weeks |

IIVST = Intensified intravenous steroid therapy; CyA = cyclosporine A; IFX = infliximab; Tacro = tacrolimus; RCT = randomized controlled trial; db = double-blind; pc = placebo-controlled; DA = drop-out; P = placebo; M-pred = methylprednisone.

Medical Treatment of Uncomplicated Severe Ulcerative Colitis

Patients with severely active UC can be treated initially with oral corticosteroids. Those patients failing may require hospitalization for administration of intravenous corticosteroids [10–12]. In patients who present as steroid-refractory UC or treatment failure, CMV colitis has to be excluded by sigmoidoscopy with biopsies. It is believed that CMV colitis might be responsible for treatment failures in UC patients in up to 10% [13]. Cyclosporine, infliximab, and tacrolimus are used as rescue therapy in patients with severe UC who fail intravenous corticosteroids [14–18]. All three therapies are graded as evidence level EL1b in intravenous-steroid resistant UC of any extent in the new ECCO guidelines [8]. The different medical treatment modalities (steroids, cyclosporine, infliximab, and tacrolimus) will be discussed in the following section and a summary of those studies can be found in table 1. A special focus was posed on the age range of patients who have been included in the respective studies. Table 2 summarizes the most relevant statements regarding elderly patients with severe UC.

Steroids

Steroids are efficacious in UC and severe attacks of UC are treated with intensified intravenous steroid therapy (IIVST). The first placebo-controlled trial on steroid therapy in severe UC was reported by Truelove and Witts [10] in 1955. In this trial, remission was achieved in 41%, response in 27% and no change/worse outcome was noted in 31% of patients, respectively (table 1). Despite this established treatment, severe flares of UC have a high colectomy rate varying from 38 to 47% [11, 19]. Of patients with UC affecting the entire colon, up to 60% have been reported to have surgery within three months [19]. However, this may vary from country to country. Colectomy rates especially in northern Europe are higher as compared to central and southern Europe. Clearly colectomy rates in Switzerland are lower in newly diagnosed pancolitis.

In 1974, Truelove and Jewell [11] described the Oxford regimen for the treatment of severe UC (table 1). This regime is essentially based on the use of intravenous corticosteroids (hydrocortisone 100 mg 4×/day or methylprednisone 60–80 mg/day with hydrocortisone 100 mg rectally/day), the meticulous monitoring of patients and clear decision making concerning surgery [11, 12]. It was reported that 60% of patients had a complete response

Table 2. Statements regarding elderly patients with UC

UC patients present with an age-specific incidence rate with a second peak occurring at 60–70 years [1]

In elderly patients with UC, there is a higher rate of corticosteroid-dependent patients leading to an increased requirement of immunosuppressive treatment [25]

UC patients older than 50 years need renal function tests before starting cyclosporine therapy [30]

Elderly UC patients either tend to have proctitis or limited left-sided colitis [1, 26] or present with a severe initial episode with toxic megacolon [6]

Early surgical interventions are recommended for elderly patients with severe UC [1, 2]

and 15% showed improvement to this therapy [12]. The lack of improvement to this intensive therapy by day 5 is considered an absolute indication for emergency colectomy [11–12, 20]. In a systematic review of 32 trials of steroid therapy for acute severe UC involving 1,991 patients from 1974 to 2006, the overall response to steroids (intravenous hydrocortisone, methylprednisolone, or betamethasone) was 67% [21]. The ECCO consensus on UC grades intravenous steroid therapy as evidence level EL1b [8].

Studies conducted to compare different types of steroids and adrenocorticotrophic hormone did not demonstrate any clear advantage of one type versus the others [22–24]. Regarding elderly patients, there is only one case-control Spanish study, which included patients older than 60 years (8 patients with CD and 25 patients with UC). The authors found a higher rate of corticosteroid-dependent patients leading to an increased requirement of immunosuppressive treatment in the elderly group [25]. The Italian Colon-Rectum Study group reported on 1,705 patients with UC. In this cohort 436 patients were under 25 years old and 386 patients were over 50 years old. Interestingly, younger patients tended to have a greater anatomical-clinical severity with greater use of steroids in the acute phase of UC [26].

Cyclosporine A

Promising results from uncontrolled trials [27, 28] were substantiated by a two-center, randomized, placebo-controlled trial from North America in which intravenous cyclosporine at a dose of 4 mg/kg was given to UC patients not responding to intravenous steroids. An ini-

tial response rate of 82% was described within a mean time to response of 7 days, versus 0% in the group that received steroids alone (table 1) [14]. In the past decade, a few controlled trials and many case series confirmed that intravenous cyclosporine at a dose of 2–4 mg/kg/day induces clinical remission in over 50% of the patients in the short term so that colectomy can often be avoided [14–16, 29]. Cyclosporine has been shown to be at least as effective as corticosteroids in a double-blind controlled trial comparing i.v. cyclosporine with i.v. corticosteroids as monotherapy for a severe attack of UC [15]. The same group also reported a randomized, double-blind study comparing 4 versus 2 mg/kg intravenous cyclosporine. The study showed that the higher-dose cyclosporine has no additional clinical benefit over lower-dose cyclosporine in the treatment of severe attacks of UC. Although differences in adverse events were not observed, it was concluded that because most cyclosporine-associated adverse events are dose dependent, the use of 2 mg/kg should improve the long-term toxicity profile of the agent [16]. Although the value of cyclosporine for the management of severe UC has been accepted in most referral centers, concerns about toxicity have prevented its use in many hospitals. Cyclosporine can lead to side effects such as hypertension, renal failure, hypertrichosis and neurotoxicity, which lead to death in some patients, thus limiting its use. However, with the continuous i.v. treatment over 24 h such deleterious events have never been reported. Especially patients older than 50 years are more likely to have impaired renal function and must therefore have an accurate quantification of creatinine clearance before cyclosporine therapy is started [30]. The benefit of avoiding colectomy therefore needs to be balanced against the risk of inducing profound immunosuppression and severe side effects.

Long-term prognosis with cyclosporine therapy is reported to be improved by the introduction of azathioprine or mercaptopurine on discharge from the hospital in association with oral cyclosporine as bridging therapy [31]. Cyclosporine is typically discontinued after 3–4 months, the time window which azathioprine needs to start its delayed action [32]. It is even debatable if cyclosporine treatment should be given to a patient who has proven azathioprine resistance or intolerance. A recent systematic Cochrane review on severe UC has shown that the evidence indicating that cyclosporine is more effective than standard corticosteroid therapy is weak, and that cyclosporine does not avoid the overall need for colectomy [33]. This Cochrane analysis states that ‘the long-term benefit is unclear, when adverse events such as cy-

closporine-induced nephrotoxicity may become more obvious’. Most institutions have therefore restricted the use of cyclosporine to patients whose disease is refractory to corticosteroids, given the important risk of toxicity and the high cost of cyclosporine. Although there is a risk of relevant drug toxicity, most patients will opt for cyclosporine if offered, rather than undergo colectomy. A study from Cohen et al. [34] assessed 42 patients who received cyclosporine during an acute severe relapse. They found that patients who retained their colon felt physically and psychologically healthier with a significantly better quality of life compared with those who had undergone colectomy. On the basis of these observations, the systematic use of cyclosporine in severe UC is still debated. Moreover, retrospective series showed that, despite an initial response to cyclosporine, many patients would eventually undergo proctocolectomy a few years down the line [35].

Infliximab

More than 15 years ago, the potent anti-inflammatory effects of anti-tumor necrosis factor (TNF) therapy with the chimeric antibody infliximab were shown in Crohn’s disease, in rheumatoid arthritis and later also in UC. Six randomized controlled trials were performed to the present date for evaluation of induction of remission in patients with UC [17, 36–40]. Four studies compared infliximab to placebo [17, 36, 39, 40], one study compared infliximab to oral steroids [38] and the other to intravenous corticosteroids [37]. A small placebo-controlled trial reported in 2001 [40] recruited 11 patients failing 5 days of i.v. steroids to receive a single dose of infliximab or placebo. Four of the eight patients receiving infliximab were deemed treatment success at 2 weeks versus none of the three patients given placebo. The trial was not continued because of recruitment difficulty. A Scandinavian multicenter randomized placebo-controlled trial has recently shown that infliximab given as a single 5 mg/kg infusion was significantly more effective than placebo. In this study, 29% (7/24) of the patients in the infliximab group had a colectomy within 90 days (primary end point), compared with 67% (14/21) in the placebo group, and this is a statistically significant difference ($p = 0.017$) [17]. The study, however, refers to a follow-up of 3 months and provides no information on the long-term follow-up. Two large studies, called ACT1 and ACT2, evaluated each 364 patients with active UC. Patients were randomized to intravenous infusions of infliximab at 5 mg/kg, 10 mg/kg or placebo. Response rates were reported to 69% (ACT1) and 64% (ACT2) at week 8

[36]. It should however be noted that hospitalized patients with severe colitis represent a very different population to the outpatients in the ACT1 and ACT2 studies and large controlled trials are needed as described in the ECCO guidelines [7–9].

In summary, the use of infliximab as a treatment for severe UC seems promising, but is not yet clearly defined. In particular, whether early use of infliximab will prevent colectomy is uncertain.

Tacrolimus

Only one double-blind randomized placebo-controlled study has been performed so far [8]. This trial showed after 2 weeks of treatment clinical remission in 19% (4/21) of patients in the high target serum concentration group, and in 5% (1/20) in the placebo group. Further, a statistically significant dose-dependent rate of clinical improvement at 2 weeks and a colectomy-free survival of all patients at week 10 were demonstrated. Tacrolimus may be effective for short-term clinical improvement in patients with refractory UC. It carries many of the risks including nephrotoxicity of cyclosporine.

Special Age-Related Situations in Severe Ulcerative Colitis

Toxic Megacolon

It has been suggested that UC tends to be less extensive when it develops later in life; the majority of elderly patients have proctitis or limited left-sided involvement [1, 26]. On the other hand, it has been claimed that older patients appear to be more likely to present with a severe initial episode and to develop toxic megacolon, both of which are associated with a high fatality rate. In a community-based study from Aberdeen, Scotland, 14% of patients aged over 70 had severe initial episodes, compared with 7% of younger patients [6]. The excess of severe first episodes in older patients accounted for an increased mortality rate of 19% compared with 1.7% for the entire study population.

Surgery

Early surgical intervention has been recommended for elderly patients with severe UC, because postoperative complications such as toxic megacolon, free perforation, massive hemorrhage, and mortality are more common in the elderly when surgery is delayed and performed when they are critically ill [1, 2]. It is unclear

whether the higher mortality rate in elderly patients with UC, reaching 19% in some reports, is due to the disease process itself or the adverse effects of concomitant illnesses [1]. Postponing surgery on the basis of advanced age alone may increase mortality, whereas prompt surgical intervention has been associated with dramatic reductions in mortality in elderly patients with severe colitis [41]. Nevertheless, surgery is still the definitive procedure for the treatment of UC in adult and older patients, and its timing is of paramount importance. Morbidity of severe UC results from prolonged ineffective medical treatment and therefore a delay in surgical treatment should be avoided. The surgical procedure most commonly performed in adult and older patients is a subtotal abdominal colectomy and ileostomy, followed about 3 months later (when the patient is off steroids with an improved nutritional state) by completion proctectomy and the formation of an ileal-pouch anal anastomosis (IPAA).

Conclusion

Severe UC occurring in the elderly is an important issue in the field of gastroenterology, considering that the proportion of elderly persons is increasing in our society. Sometimes, however, stoicism of the elderly patient is a formidable obstacle to early diagnosis. Severe UC must be considered a medical emergency especially in the elderly patient, even if the mortality rate for this disease is decreasing. Several factors might have contributed to the reduction in mortality that has been observed over the past 30 years, such as the widespread use of the Oxford (corticosteroid) regimen, which has now been integrated with the administration of cyclosporine and infliximab, the early detection of complications, the careful timing of surgery and the improved anesthesiological and surgical techniques. Key issues remain as to what should be first- and second-line therapies in different age groups, when surgery should be undertaken, and the risk of switching between immunosuppressants in these critically ill patients. As about 30% of severe UC cases continue to need colectomy, the timing of surgery and the collaboration between gastroenterologist and surgeon remain the most important goals in the management especially in older patients. More studies in different age groups in patients with severe UC are desperately needed and the management needs to be defined according to those studies.

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